Gastroenterologia Japonica
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Vol. 22, No. 4
Printed in Japan

—Case Report—

BEHÇET'S DISEASE ASSOCIATED WITH AMYLOIDOSIS

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Summary

A case of Behçet's disease associated with amyloidosis is reported. A 34 year-old woman was referred to our Department after suffering diarrhea for one month. She had the complete type of Behçet's disease which began development when she was 12 years old. Diarrhea disappeared after she was admitted to the hospital but stool occult blood was strongly positive. A barium enema revealed the disappearance of haustration in the left colon. Urinalysis was normal. She suffered from cholecystolithiasis, and a cholecystectomy was performed. A histopathological examination revealed amyloid deposits in the stomach, duodenum, large bowel, gallbladder, and kidney. Amyloid was indicated as AA type after treating kidney and colon sections with potassium permanganate. Upon discharge, she was free of symptoms. Up to the present time, 19 cases, including our case of Behçet's disease with amyloidosis, have been reported. Four cases in Japan have been reported in Japanese. Reviewing the 19 cases, however, all of them developed initially as Behçet's disease, followed by amyloidosis and there have only been three cases including ours where the type of amyloid was studied. Our finding was identical to the previous two reports; namely identification of the AA type which is common in secondary amyloidosis. These findings lead to a conclusion that amyloidosis associated with Behçet's disease is secondary.

Key Words: *Amyloidosis, Behçet's disease, Secondary amyloidosis.*

Introduction

More than 10 cases of Behçet's disease associated with amyloidosis have been reported[1–9], but they are mainly from Mediterranean countries where Behçet's disease is common. Here we report a case of Behçet's disease associated with amyloidosis, and discuss another four Japanese cases previously reported in Japanese[10–12]. In our case, the type of amyloid was indicated to be AA which is common for secondary amyloidosis. Ours is the third case in which the type of amyloid has been identified. Our report certifies that there have been five cases of Behçet's disease associated with amyloidosis in Japan and indicates that amyloidosis associated with Behçet's disease is secondary.

Received January 26, 1987. Accepted April 13, 1987.

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The authors wish to thank Dr. M. Ogino for referring the case, to Dr. Y. Nakamoto and Dr. K. Asakura for studying the kidney, to Dr. M. Sagishima for histopathological studies, and to Miss C. Igarashi for her skillful preparation of this manuscript.

Case Report

A 34 year-old woman with Behçet's disease was referred to our department on February

28, 1986 because of diarrhea and abdominal pain for one month. Past and family histories were noncontributory. Her clinical course is depicted in **Fig. 1**. The first symptom of Behçet's disease, aphthous stomatitis, occurred at the age of 12 (1964). She has had polyar-

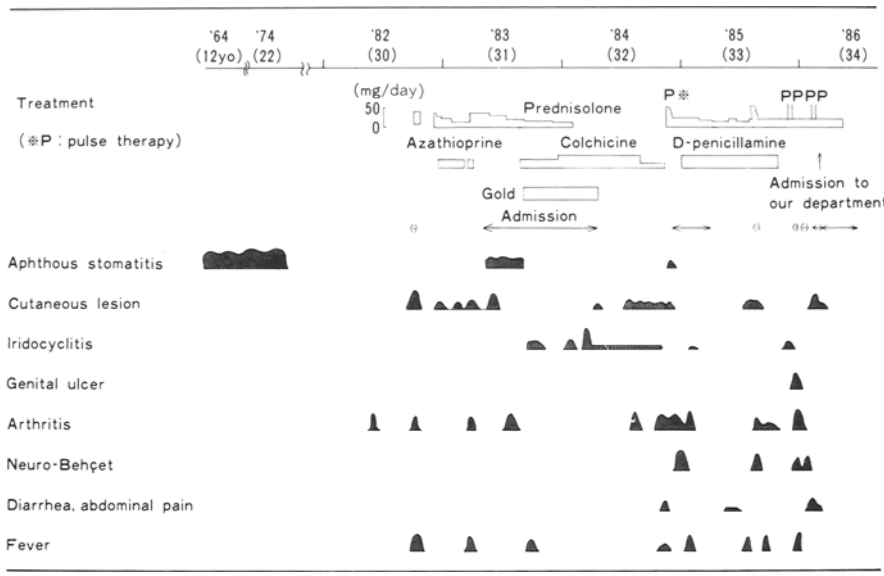
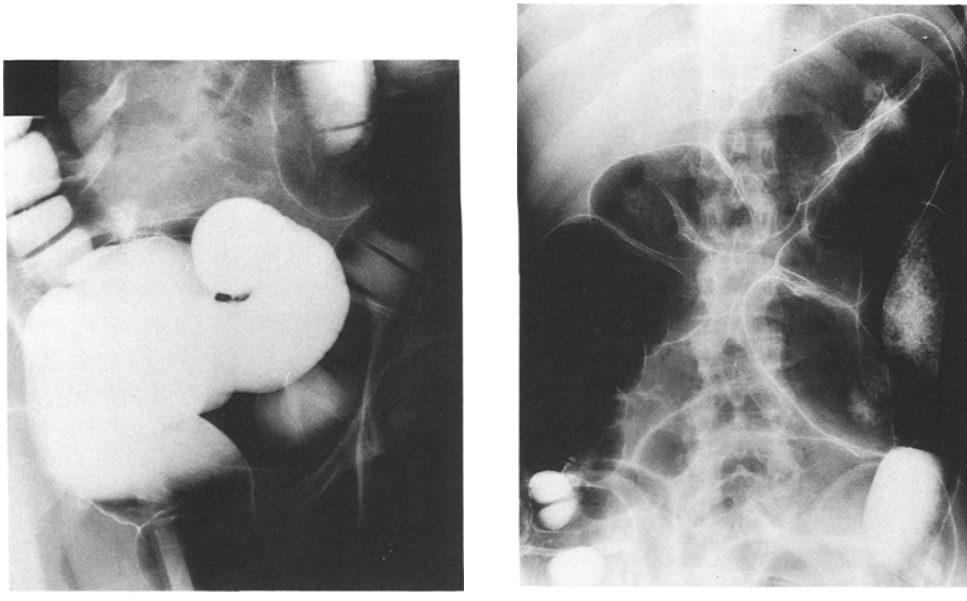


Fig. 1. Clinical course.



a b

Fig. 2. Barium enema (February 27, 1985 a. left) was unremarkable. Barium enema (March 17, 1986 b. right) showed disappearance of haustration in the left colon.

Table 1. Laboratory data

	1982	1983	1984		1985			1986		
	Dec 2	Mar 31	Apr 20	Dec 4	Mar 22	Jul 31	Dec 29	Feb 4	Feb 20	May 29
ESR 1° (mm)	85	84	113	145	122	93	94	30	30	12
Hb (g/dl)	11.8	12.1	9.9	7.6	9.9	9.2	10.2	11.6	9.7	11.7
WBC (/mm³)	11500	14900	4100	6900	7500	10900	13600	8800	7700	7800
CRP	—	+	±	±±±±	±±	±±	±±±±	±	±	—
TP (g/dl)	7.9	8.1	8.8	9.4	8.2	7.6	6.2	6.4	5.6	7.2
α_2-gl (%)	9.0	10.2	9.0	10.1	15.1	15.6	13.7	16.9	17.7	9.8
γ-gl (%)	27.1	24.9	25.5	56.8	31.7	24.0	27.4	16.3	15.4	11.5
IgG (mg/dl)	1680	1590	2976	4250	3100	*	*	*	1557	1111
Proteinuria	—	+	—	—	*	*	—	—	—	—

*: not tested

thritis, fever and erythema nodosum, iridocyclitis, convulsion and unconsciousness, and a genital ulcer during the previous four years. These symptoms fulfilled the criteria for the complete type of Behçet's disease (aphthous stomatitis, cutaneous manifestations, iridocyclitis, and genital ulcer). She had similar diarrhea twice (1984, 1985). The diarrhea in 1984 was associated with the symptoms of Behçet's disease. The other in 1985 was less intense and a barium enema study (Feb. 27, 1985) was unremarkable (**Fig. 2a**). She was admitted to hospital seven times during the past four years for the treatment of Behçet's disease. Therapies employed were prednisolone including pulse therapy, an immunosuppressive agent, Colchicine, gold, and D-penicillamine. The main laboratory data are summarized in **Table 1**. A marked increase of ESR, a strong positive CRP, hyperproteinemia due to hyper-gammaglobulinemia (elevated IgG), and hyper α_2-globulinemia, indicated intense inflammation during the course. Mild anemia had been observed. Proteinuria was transiently found on March 31, 1983. The highest titer of antinuclear factor (ANF) (320, homogenous pattern), the highest unit of anti DNA antibody (RIA 90 U/ml), and the highest value of immune complex (5.5 μg/ml) were observed from December 1984 to January 1985. These

Table 2. Laboratory data on admission

ESR 1°	30 mm	Na	136 mEq/L
Hb	9.7 g/dl	K	3.4 mEq/L
WBC	7700/mm³	Cl	99 mEq/L
Stool occult	±±	BUN	9 mg/dl
pathogens	−	CRP	±
Urinalysis	normal	α_2-gl	17.7%
TP	5.6 g/dl	IgG	1557 mg/dl
Alb	3.3 g/dl	IgA	242 mg/dl
GOT	29 U/L	IgM	202 mg/dl

were all normal in the latest study in January 1986. No abnormal results have been found in the following repeated tests: RA test, rheumatoid arthritis hemagglutinin (RAHA) test, M-protein, Wassermann's reaction, CH50, C3, C4, and anti-Smith (Sm), Sjögren's syndrome A (SS-A), Sjögren's syndrome B (SS-B), extractable nuclear antigen, mitochondria antibodies. The phenotype of HLA was A2, AW24 (9), BW52 (5), B15, and CW1.

Examinations

Physical examination was unremarkable except for stria cutis distensae in the lower abdomen. Laboratory data (**Tables 1, 2**) showed a mild elevation of ESR (1° 30 mm), mild anemia (Hb 9.7 g/dl), strongly positive stool occult blood (±±), hypoproteinemia (TP 5.6 g/dl), hypoalbuminemia (3.3 g/dl), positive CRP (±), and hyper α_2-globulinemia (17.7%). Urinalysis, serum electrolytes, and

immunoglobulins were all normal. Chest X-ray film did not show cardiomegaly and ECG was normal.

1. Studies of the large bowel

A barium enema revealed the disappearance of haustration in the left colon (**Fig. 2b**). There was no ulcer or deformity in either the cecum or the terminal ileum. Using colonoscopy a marked increase in vascularity was observed in the descending colon (**Fig. 3**). Six biopsy specimens were taken (two specimens each from three sites; the cecum, the descending colon, and the sigmoid colon) for routine histopathology, as well as for amyloid using polarized light microscopy of Congo red-stained histological preparations. Histopathologically, there were no findings indicating specific colitis. However, amyloid deposits were observed in all the colon specimens except for one cecal specimen. The deposits were found around the vessel and they were more marked in the submucosa (**Fig. 4a**). The amount of deposits was not much. Among the three sites, the descending colon showed a more amyloid deposition compared to that of the rectum or the cecum. Since amyloid deposition was found in the large bowel, amyloid deposition was studied systematically as follows.

2. Studies of the upper gastrointestinal tract

Alimentary examination showed a delayed transit time of the esophagus. The antrum showed granular changes and the duodenum was slightly distended (**Fig. 5**). The granular changes of the antrum were also seen by endoscopy (**Fig. 6**). In the bulb and the second portion of the duodenum, various endoscopic changes such as irregularity of the vascular pattern (**Fig. 7a**), redness (**Fig. 7b**), whitish mucosa (**Fig. 7c**), and redness of the papilla of Vater (**Fig. 7d**) were observed. Histopathological findings from the granular area of the antrum and the duodenum were unremarkable except for the amyloid deposition. In the antrum, numerous amyloid depositions were observed (**Fig. 8**). Amyloid fibril was also dem-

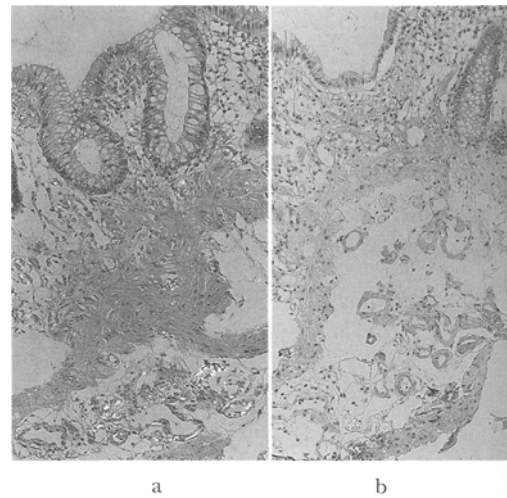


Fig. 4. Tissue section of the discending colon was stained with Congo red and observed by polarized light microscopy. Refractile materials (amyloid) were observed mainly around vessels in the submucosa (a. left). Such materials were not observed after treatment of section with potassium permanganate (b. right).

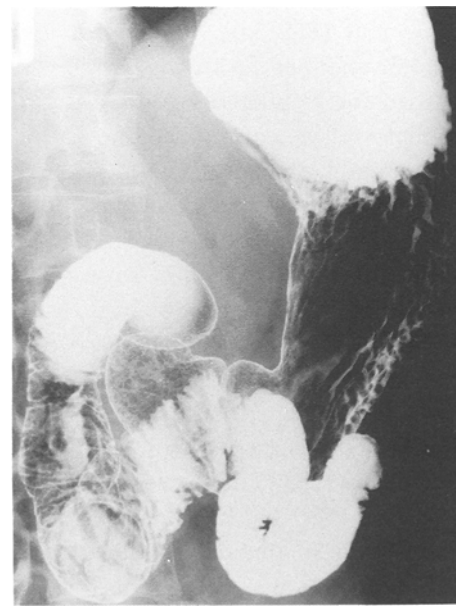


Fig. 5. Gastrofluoroscopy showed granular changes in the antrum and slight distension in the duodenum.

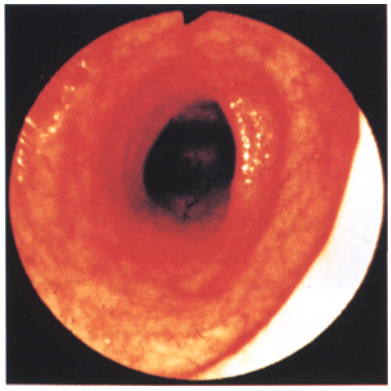


Fig. 3. Colonoscopy revealed a marked increase in vascularity in the descending colon.

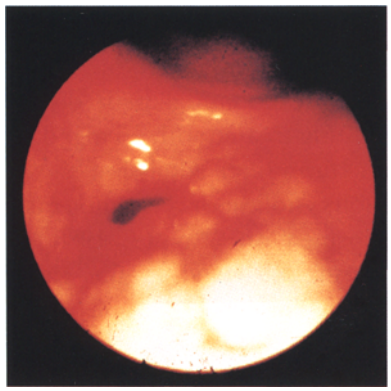


Fig. 6. Endoscopy of the stomach revealed granular changes in the antrum.

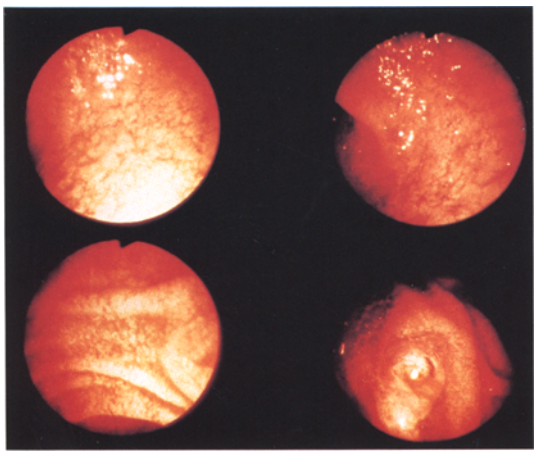
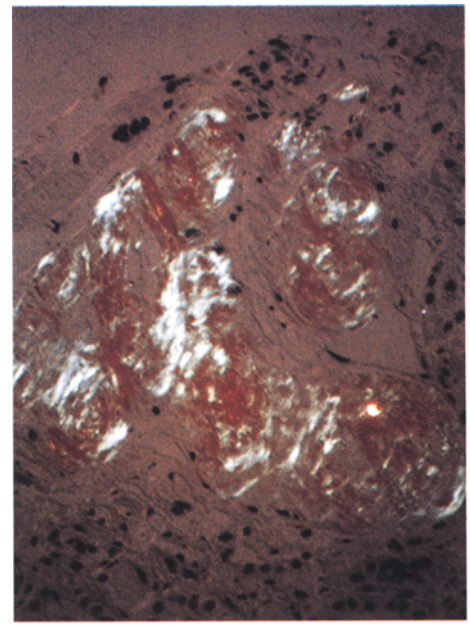
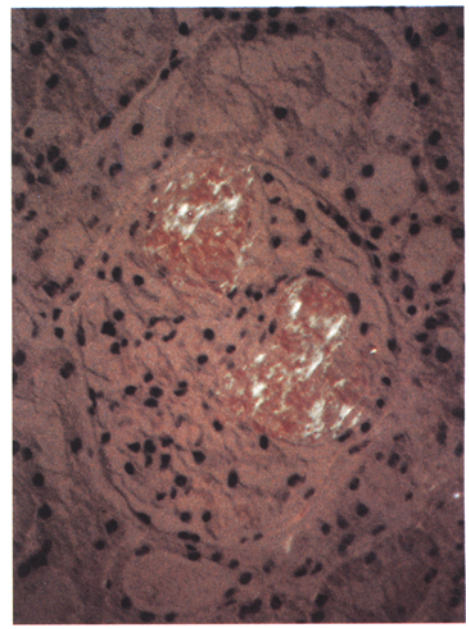


Fig. 7. Endoscopy of the duodenal bulb and the second portion of the duodenum demonstrated an irregularity of vessels (a. left upper), redness (b. right upper), whitish mucosa (c. left lower), and redness of papilla of Vater (d. right lower).



a



b

Fig. 9. Tissue section of the kidney was studied for amyloid deposits. Refractile materials (amyloid) were observed around vessels (a. upper) and in the glomeruli (b. lower).

onstrated electromicroscopically in the duodenal specimen. Biopsy specimens were not obtained from the area showing redness in the papilla of Vater.

3. Radiologic examination of the small bowel

The double contrast method by means of duodenal intubation and administration of barium and air was employed. The transit time of the contrast medium in the small bowel was prolonged for two and a half hours. However, neither stenosis nor ulcer was found in the small bowel.

4. Echo of the abdomen and echo cardiogram

Multiple small stones were observed in the gallbladder. Liver, pancreas, kidney, spleen, and heart were normal.

5. Endoscopic retrograde cholangiopancreatography

Multiple small stones were observed in the gallbladder. The time for the excretion of contrast material from the gallbladder was delayed.

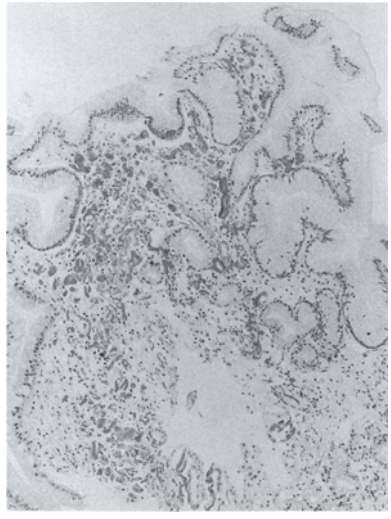


Fig. 8. Congo red stained materials were seen in the mucosa obtained from the granular area of the antrum. They were refractile under polarized light.

6. Laparoscopy and liver biopsy

Laparoscopy revealed a normal appearance of liver and amyloid deposition was not found in the biopsy specimen.

7. Kidney biopsy

Amyloid deposits were found around the vessels (**Fig. 9a**) and in some of the glomeruli (**Fig. 9b**).

8. Study of the types of amyloid

Treatment of sections from the colon and the kidney with potassium permanganate resulted in the complete disappearance of the affinity of the amyloid for Congo red (**Fig. 4b**). This indicated AA type amyloid[13].

Clinical course

When she was admitted to our department, diarrhea and abdominal pain disappeared. She was being treated with 15 mg/d. of prednisolone. During her admission she suffered from cholecystolithiasis. A cholecystectomy was performed on May 14, 1986. Amyloid deposits were observed in the gallbladder. Stool occult blood has become only weakly positive since April, 1986. The laboratory data on May 29 did not indicate any inflammation (**Table 1**). Hypoproteinemia and anemia were improved. She was discharged on June 2 receiving 14 mg/d. of prednisolone. She was referred to her previous doctor and the dosage of prednisolone was gradually decreased. She has been well until now (Jan. 16, 1987) except for one flare-up of Behçet's disease which promptly responded to prednisolone.

Discussion

Our case encountered relentless flare-ups of Behçet's disease. She was admitted to hospital seven times during the previous four years. Amyloid deposits were found in the stomach, duodenum, large bowel, gallbladder, and kidney. They were not found in the liver and echo cardiogram did not indicate amyloidosis. Beroniade et al.[1,2] first reported two cases of

Behçet's disease associated with amyloidosis. Heretofore, 19 cases, including our case, have been reported (**Table 3**)[1–12]. Eleven of these are from Mediterranean countries[3–5,7–9] and five are from Japan[10–12]. Four cases from Japan have been reported in Japanese, but have not been cited in English literature. The existence of several cases of Behçet's disease associated with amyloidosis in Japan seems to deny the concept suggested by Dilsen et al.[4] that the association of amyloidosis with Behçet's disease is genetically influenced. Reviewing the 19 cases, the ages are found to range from 13 to 70 years. Male and female subjects, as well as both incomplete and complete types of Behçet's disease were affected. The interval of time between the onset of Behçet's disease and the diagnosis of amyloidosis was from 3 to 26 years. Amyloid deposits were most frequently found in the kidney. Amyloid deposits in the gastrointestinal tract were reported in about half of the 19 cases.

It is uncertain whether amyloidosis is associated with Behçet's disease incidentally or secondarily, although recent observations by Skinner et al[6] and Peces et al.[9] have shown AA type amyloid in such associated cases, indicating secondary amyloidosis. Reviewing the 19 cases, we could not find any case where amyloidosis initially appeared and then was followed by Behçet's disease. This clinical observation clearly suggests that amyloidosis is secondary. Our case was the third in which AA type amyloid was indicated. These observations lead to the conclusion that amyloidosis is secondary due to the inflammation of Behçet's disease.

Amyloidosis was most frequently life-threatening[2,3,8,10,14]. Our case had neither nephrotic syndrome nor progressive diarrhea and this indicates that our case will survive for some time.

Table 3. Behçet's disease associated with amyloidosis

Authors	Age	Sex	Origin or Country	Behçet's disease		Amyloid deposition		
				Type*	Duration**	Kidney	GI tract***	Type
Beroniade[1,2]	nd	nd	Rumanian	nd	nd	+	+ (I)	
	nd	nd		nd	nd	+	nd	
Rosenthal et al.[3]	19	m	Jewish	C	3y	+	nd	
	14	m	Arab	I	3	+	+ (R)	
	38	m	Jewish	I	3	+	nd	
Dilsen et al.[4]	33	m	Turkey	C	26	+	nd	
	46	m		I	7	+	nd	
	31	m		C	15	+	nd	
Jimi et al.[10]	35	m	Japanese	I	19	+	+ (S,D,R)	
Watanabe et al.[11]	54	m		I	19	nd	+ (C)	
	70	f		I	10	+	+	
Hamza et al.[5]	27	f	Tunisia	I	9	+	nd	
Tanaka et al.[12]	45	m	Japanese	I	7	+	+ (R)	
Skinner et al.[6]	33	f	USA (Black)	C	21	+	nd	AA
Penza et al.[7]	13	f	Italy	I	8	+	+ (R)	
Sozen et al.[8]	33	m	Turkey	C	9	nd	+ (R)	
	43	m		I	3	nd	+ (D)	
Peces et al.[9]	36	m	Spanish	I	9	+	nd	AA
Our case	34	f	Japanese	C	22	+	+ (S,D,C,R)	AA

*C: complete, I: incomplete nd: not described

**years between the onset of Behçet's disease and the diagnosis of amyloidosis

***S: stomach, D: duodenum, I: intestine, C: colon, R: rectum

Amyloidosis of the alimentary tract exhibits various roentgenologic and endoscopic findings. Granular changes (stomach), whitish mucosa or redness in mucosa, dilatation of the duodenum (small bowel), disappearance of haustration (large bowel), abnormal vascularity (small and large bowel), and delayed motility (esophagus, small bowel) found in our case have been described in amyloidosis[15–17]. Gastrointestinal bleeding from positive stool occult blood to frank hemorrhage was also demonstrated as one of the symptoms in amyloidosis of the alimentary tract[14–20]. In our case marked stool occult blood persisted during the initial period of the admission but became weakly positive later. Recently amelioration in the stool occult blood in amyloidosis, as found in our case, has been reported[19,20].

The most common intestinal complication of Behçet's disease is deep ulcers which are liable to perforate or penetrate in the ileocecal area[21,22]. This complication often requires surgical treatment. One hundred and thirty-six surgical cases in the Japanese literature have been recently reviewed[22]. Much less frequently, various forms of diffuse colitis have been reported as a complication of Behçet's disease[23–26]. Now, intestinal amyloidosis is to be added to the list of intestinal complications of Behçet's disease. Since the concept of secondary amyloidosis in Behçet's disease has not been established before, papers dealing with diffuse colitis do not mention studies for amyloid deposition[23–26]. Some of the cases with colitis have friable bleeding mucosa or a loss of haustration, which can be seen in intestinal amyloidosis. Therefore, colitis in Behçet's disease should be studied for possible secondary amyloidosis. Although the frequency of association of amyloidosis to Behçet's disease is low; 3.1% and 5.9% according to Dilsen et al.[4] and Rosenthal et al.[27] respectively, we must keep in mind secondary amyloidosis as a complication of Behçet's disease showing gastrointestinal symptoms.

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